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Association of Polymorphisms of Serotonin Transporter (5HTTLPR) and 5-HT2C Receptor Genes with Criminal Behavior in Russian Criminal Offenders

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Keywords
Aggression · Prisoners · Serotonin transporter · 5-HT2C receptor · Genotype

Abstract
Background: Human aggression is a heterogeneous behavior with biological, psychological, and social backgrounds. As the biological mechanisms that regulate aggression are components of both reward-seeking and adversity-fleeing behavior, these phenomena are difficult to disentangle into separate neurochemical processes. Nevertheless, evidence exists linking some forms of aggression to aberrant serotonergic neurotransmission. We determined possible associations between 6 serotonergic neurotransmission-related gene variants and severe criminal offenses. ***Methods:*** Male Russian prisoners who were convicted for murder ($n = 117$) or theft ($n = 77$) were genotyped for variants of the serotonin transporter (5HTTLPR), tryptophan hydroxylase, tryptophan-2,3-dioxygenase, or type 2C (5-HT2C) receptor genes and compared with general-population male controls ($n = 161$). Prisoners were psychologically phenotyped using the Buss-Durkee Hostility Inventory and the Beck Depression Inventory. ***Results:*** No differences were found between murderers and thieves either concerning genotypes or concerning psychological measures. Comparison of polymorphism

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distribution between groups of prisoners and controls revealed highly significant associations of 5HTTLPR and 5-HTR2C (rs6318) gene polymorphisms with being convicted for criminal behavior. ***Conclusions:*** The lack of biological differences between the 2 groups of prisoners indicates that the studied 5HT-related genes do not differentiate between the types of crimes committed.

Introduction

Behavior can be considered a mechanism where the brain manages input to create a specific output, which enables the organism to adapt to changed circumstances within its biosphere. In order to survive as an individual and a species, even humans' oldest animal ancestors must have been capable of obtaining food, water, warmth, territory, mating partners, and comfort or they must have been able to show a behavioral repertoire to escape from threat, the incapacity of having offspring, heat, cold, and other forms of distress [1]. Aggressive behavior is undoubtedly one of the most important conducts to accomplish these goals. However, as aggression is involved in both reward-seeking and adversity-fleeing behaviors, it necessarily represents a heterogeneous phenomenon. Throughout the animal kingdom, a similar set of aggressive behaviors can be distinguished which are employed to obtain these goals. However, in humans an extra capacity contributes to these ends. In humans, every sensory input and behavioral output can be replaced by abstract language symbols. The human mind can create a virtual world that is intermingled with the physical world, hence creating a unique human biosphere. Part of this virtual world is condensed in specific religious rules or country legislations. This complicates the study of the types and mechanisms of human aggressive behavior. Moreover, some of these kinds of offensive behaviors can be studied in animal models and others only in healthy human volunteers or patients.

Of all of the neurotransmitters, serotonin (5-hydroxytryptamine; 5-HT) has been especially associated with the occurrence of different types of aggression. The brain 5-HT system is one of the most expansive neurotransmitter systems. 5-HT is synthesized from the essential amino acid L-tryptophan. Tryptophan hydroxylase 2 (TPH2) is the key and specific enzyme of 5-HT synthesis in the brain [2, 3]. Synthesized 5-HT is stored in synaptic vesicles and released into the synaptic cleft and it interacts with 14 types of postsynaptic 5-HT receptors [4]. The released 5-HT is reuptaken from the synaptic cleft by the plasma membrane 5-HT transporter (5HTT) into presynaptic 5-HT neurons [5] where the neurotransmitter is either taken up by storage vesicles or oxidized to 5-hydroxyindoleacetic acid by monoamine oxidase A (MAO A) [6].

A vast body of experimental evidence has demonstrated a significant role of the genotype in the predisposition to aggressive behavior [7] and implicated brain 5-HT in the control of different kinds of animal aggressive behaviors [8–12]. The data concerning human aggression is more limited. Some clinical evidence associates impulsivity and aggression with central 5-HT activity [13–15]. However, the true relevance of a dysfunction of the 5-HT system for the mechanism of human aggression has been disputed [16]. The controversy may be due to 5-HT playing a role in almost every integrative function of the central nervous system, such as mood, anxiety, stress, aggression, feeding, cognition, and sexual behavior [9]. The increase or decrease in 5-HT levels, therefore, has multiple, partly opposite, effects and the same is true for the acute and chronic effects of drugs that increase 5-HT levels [17]. This can be illustrated by regulatory role-playing by 5-HT neurotransmission within the adversity-fleeing as well as the reward-seeking systems [18]. Chronic administration of 5-HT level-increasing drugs results in downregulation of the sensitivity of 5-HT receptors [18, 19]. Moreover, the activities of the reward-seeking and adversity-fleeing systems are reciprocally coupled to one another [18]. Aggressive behavior can be facilitated by both systems, with an emphasis on offensive and defensive aggression, respectively. Adversity-fleeing aggressive behavior is primarily related to anger/fear-type behavioral stress responses increasing the activity of the amygdaloid-hippocampal activity [18]. Activation of the hippocampus and the amygdala as a reaction to anticipation of a monetary loss has been demonstrated in healthy human subjects [20]. Fibers of 5-HT neurons located at the dorsal raphe nucleus regulate acute adversity-avoidance behavior by stimulating 5-HT2C receptors (HTR2C) in the basolateral amygdala in rats [21, 22]. These findings support the notion of a regulatory role of the amygdaloid-hippocampal complex inducing the activation of an adversity-fleeing stress response by activation of 5-HT terminals coming from the dorsal raphe nucleus. Disinhibition of the amygdala by prefrontal dysfunction (organic or pharmacologically induced) and/or increased sensitivity of the amygdala due to genetic or environmental causes may result in an increased prevalence of serious aggressive incidents (including [para]suicide and homicide).

Ample evidence suggests that variations of genes modifying the functionality of 5-HT receptors, MAO A and 5-HT transporter (5HTT) may be relevant for impulsive-aggressive behavior and suicide [23–25], and associations between polymorphisms of these genes and impulsive-aggressive behavior and suicide have been shown [23, 24, 26, 27].

At least 17 molecules (TPH2, MAO A, 5HTT, and 14 serotonin receptors) regulate the serotonin synapse activity. Functional mutations in the genes coding these molecules are considered to be able to modulate 5-HT-related behavior. A common functional polymorphism, i.e., –703G>T in the human *TPH2* gene, has been reported to be associated with numerous psychiatric disorders [28].

It has been shown that the G allele and the G/G genotype of the common functional polymorphism –1019C>G (rs6295) in the human 5-HT1A receptor gene (HTR1A) could be associated with an increased risk of suicidal and impulsive behavior [29, 30].

Another receptor gene polymorphism that has been extensively investigated is the Cys23Ser variant (rs6318) of the 5-*HT2C receptor* gene (HTR2C) located on the extracellular N-terminus of the receptor, potentially altering the protein's structure or stability by eliminating a disulfide bond [31]. The HTR2C gene is located on the X chromosome (Xq24 site), which means that males are hemizygous for cysteine (G) or serine (C) in the 23rd position [32].

Two common functional VNTR polymorphisms, 5HTTLPR and STin2 in the promoter and the 2nd intron of the human 5HT transporter gene (SCL6A4), are known. The first includes 16 (long; L) or 14 (short; S) repeats of 22 bases [33, 34], while the second includes 12 (long) or 10 (short) repeats of 17 bases [35]. The short (S) allele reduces the SCL6A4 gene expression [36, 37]. The long allele (L) of the 5HTTLPR polymorphism is prevalent in Caucasians. There are numerous data associating the 5HTTLPR polymorphism with antisocial behavior, aggression and violence [38–40], alcohol [41, 42] and drug [43] addiction, and suicide [44], but also with positive characteristics such as creativity [45].

Tryptophan 2,3-dioxygenase (TDO2) catalyzes the first and rate-limiting step of the kynurenine pathway of the tryptophan metabolism and therefore affects serotonin synthesis [46].

The current study focuses on investigation the role 5-HT-related gene polymorphisms in human aggression. It was hypothesized that prisoners who had committed a murder carried polymorphisms of key genes encoding 5-HT neurotransmission different from criminal offenders who were convicted for theft. A psychological evaluation was used to assess aggression-related traits by applying the Buss-Durkee Hostility Inventory (BDHI) and depression was assessed with the Beck Depression Inventory (BDI) in order to reveal any association with genetic polymorphisms.

Table 1. Sociodemographic characteristics of the participants

Variable	Murderers (n = 117)	Thieves (n = 77)
Age, years	38±0.99	31±0.7
Age at first conviction, years	17±0.3	19±0.2
Convictions, *n*	3 (2–3)	3 (3–4)
Sentence length, years	13.6±0.6	7±0.4
Time spent in prison, years	5±0.3	1.9±0.2
Marital status		
Unmarried	78 (66.7)	39 (50.6)
Married	5 (4.3)	4 (5.2)
Divorced	25 (21.4)	22 (28.6)
Cohabitating	9 (7.7)	12 (15.6)
Education		
Primary school	48 (41)	33 (42.9)
Secondary special education	68 (58.1)	42 (54.5)
Other	1 (0.9)	2 (2.6)
Convictions of next of kin, %	52 (44.4)	63 (81.8)

Values are presented as means ± SD, medians (range), or numbers (%).

Subjects and Methods

Subjects

The work described in this article was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki of 1975, revised in Fortaleza, Brazil, in 2013) for experiments involving humans. We examined a group of 194 criminal recidivists, consisting of 117 males convicted at least once for murder and 77 males who were only convicted for theft. During the examination all of the participants were serving a prison sentence in the Kemerovo State Correctional Facility (Kemerovo, Russia). One hundred sixty-one healthy male volunteers with no criminal record (aged 32.8 ± 2.5 years) comprised the control group. All of the participants were Caucasian, specifically Russian. Sociodemographic data is presented in Table 1.

Ethical Committee

Written informed consent was obtained from each participant after obtaining approval for this study from the Local Bioethics Committee of the Mental Health Research Institute. Participation or refusal to participate was without any consequences for their detention or position in prison, and this was explicitly explained to all of the participants as part of the informed consent. None of

Table 2. Distribution of serotonin-related gene polymorphisms

Polymorphism	Genotype	Criminals (n = 194)	Controls (n = 161)	HWE		Comparison with the control group with Bonferroni correction
				criminals	controls	
5HTTLPR in *SLC6A4*	L/L L/S S/S	44 39.4 16.6	26.8 51.8 21.4	$\chi^2 = 4.24$ $p = 0.03$	$\chi^2 = 0.47$ $p = 0.99$	**$\chi 2 = 10.8$** **$p = 0.024$**
STin2 in *SLC6A4*	10/10 12/10 12/12	20.7 41 38.3	23.5 48.1 28.3	$\chi^2 = 4.51$ $p = 0.03$	$\chi^2 = 0.09$ $p = 0.82$	$\chi^2 = 3.8$ $p = 0.148$
–1019C>G (rs6295) in *HTR1A*	C/C C/G G/G	23.8 46.5 29.7	19.8 52.4 27.8	$\chi^2 = 0.8$ $p = 0.36$	$\chi^2 = 0.37$ $p = 0.6$	$\chi^2 = 1.07$ $p = 0.58$
–703G>T (rs4570625) in *TPH2*	T/T G/T G/G	57.2 37.6 5.2	62.5 33.3 4.2	$\chi^2 = 0.2$ $p = 0.65$	$\chi^2 = 0.51$ $p = 0.94$	$\chi^2 = 0.97$ $p = 0.614$
rs6318 in *HTR2C*	G C	83.6 16.4	94.4 5.6			**$\chi 2 = 10$** **$p = 0.012$**
rs2271537 in *TDO2*	A/A A/C C/C	24.7 43.0 32.3	26.8 43.9 29.3	$\chi^2 = 3.38$ $p = 0.06$	$\chi^2 = 1.2$ $p = 0.27$	$\chi^2 = 0.27$ $p = 0.87$

Values are presented as numbers unless otherwise stated. HWE, Hardy-Weinberg equilibrium. Bold is only used to highlight those cases with p value <0.05 for the convenience of readers.

the participants had a compromised capacity/ability to consent; thus, consent from the next of kin was not necessary and not recommended by the local ethics committee. All findings were dealt with anonymously and were not reported back to the participants or staff.

Phenotypic Measures

Clinical and demographic data were extracted from the participants' files. Aggression-related traits were assessed using the BDHI, which includes 10 subscales (i.e., physical aggression [assault], indirect hostility, irritability, negativism, resentment, suspicion, verbal hostility, guilt, hostility index, and aggression index). Depression level was assessed with the BDI. BDHI and BDI self-assessments were supervised and checked by a clinical psychologist.

Blood Sample Collection

Blood samples were obtained from the participants via antecubital venipuncture. DNA was extracted from venous blood on a glass sorbent using a Medigen DNA extraction kit (Medigen, Russia) according to supplied protocol. The DNA concentration of the obtained samples ranged between 15 and 200 ng/μL. Isolated DNA samples were kept at −20 °C until analysis.

Genotyping

Based on previously obtained data and literature evidence we selected the following polymorphisms: 5HTTLPR and VNTR-17 (STin2) in the *5HTT* gene, –703G>T (rs4570625) in the *TPH2* gene, –1019C>G (rs6295) in the *HTR1A* gene, rs6318 in the *HTR2C* gene, and rs2271537 in the *TDO2* gene. During SNP selection we were guided by 2 rules: (1) the SNP must be functional and (2) the frequencies of both alleles must be near 50% (to provide the maximal number of each genotype). Hence, there existed a sufficient chance that such a polymorphism would be associated with a clinical difference when the corresponding protein was relevant for mediation of this effect.

Using suitable primers, 5HTTLPR and VNTR-17 (STin2) in the *5HTT* gene were investigated via AFLP analysis [36, 45]. Polymorphisms of 703G>T (*TPH2* gene) and 1019C>G (*HTR1A* gene) were determined using an allele-specific PCR. To increase the specificity of the PCR, noncomplementary nucleotides were introduced in the 3′ position from the 3′-end of suitable allele-specific primers. Therefore, the PCR product was efficiently amplified only if the 3′-end nucleotide was complementary to genomic DNA. PCR was performed with a Verity™ thermocycler (Applied Biosystems, USA). PCR products were visualized by ethidium bromide staining in 2% agarose gel. The length of the amplicons was determined with a pBluescriptSK/MspI marker.

Genotyping of rs2271537 in the *TDO2* gene and rs6318 in the *HTR2C* gene was performed with allele-specific real-time PCR using an Applied Biosystems-designed kit. Amplification was performed with a StepOnePlus cycler (Applied Biosystems), and the results were analyzed with cycler-supplied software.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0. The χ^2-test was used for Hardy-Weinberg equilibrium and genotype distribution comparison. Bonferroni correction for multiple comparisons was used for the χ^2-test of SNP frequencies. Since the primary outcome of this paper was to assess the difference in polymorphism frequencies between criminals and controls, calculation of Bonferroni correction value was performed using the formula $p < 0.05/m$, where m is the number of independent tests (in our case, $m = 6$, as far as 6 genomic loci were analyzed). G*Power 3 software was employed for the power analysis of χ^2-tested genotype distribution comparisons. The secondary outcome of this paper was to analyze associations of psychological data in criminals with different genotypes. Spearman's rank coefficient was used to evaluate the correlation between psychological scales. As scales of the BDHI were correlated to each other (data not shown), genetic associations with psychological data were assessed by MANOVA. The Kruskal-Wallis test with following a Mann-Whitney test with Bonferroni correction was also applied.

Results

The power analysis showed that, in the case-control analysis, for 5HTTLPR in SLC6A4 we had sufficient power (i.e., 0.99) to detect a medium effect size of $w = 0.34$, whereas for STin2 in SLC6A4 and for rs6318 in HTR2C we had sufficient power (i.e., 0.97 and 0.99, respectively) to detect a small effect size of $w = 0.21$ and $w = 0.27$, respectively.

No association of –703G>T, –1019C>G, STin2, and rs2271537 polymorphisms in the TPH2, HTR1A, SLC6A4, and TDO2 genes with criminal, aggressive (BDHI), or depressive (BDI) features was observed (Table 2).

At the same time, comparison of polymorphism distribution between the groups of prisoners and controls revealed an association of 5HTTLPR in the SLC6A4 gene (OR = 1.55; 95% CI 1.15–2.10; $p = 0.004$) and rs6318 in the HTR2C gene (OR = 3.31; 95% CI 1.52–7.21; $p = 0.0026$) with being convicted for criminal behavior. An increase in the frequencies of the L allele and the L/L genotype of 5HTTLPR and the C allele of the rs6318 polymorphism in the imprisoned criminals compared with the control group was revealed.

In order to gain a more detailed insight into the nature of the relationship between 5-HT-related gene polymorphisms and aggression-related psychological traits, an analysis of its associations was performed. Firstly, the relationship between BDHI and BDI scores and age, time spent in prison, and total sentence was tested using the Spearman correlation coefficient and it was not found to be significant ($p > 0.05$). Thus, age, time spent in prison, and total sentence were not used as covariates in all association analyses.

Tables 3 and 4 summarize the results of phenotypic data as a function of each SNP analyzed. Carriers of the rs6318 G genotype showed a higher score on the "negativism" scale of BDHI in comparison to more subjects in the group of criminals being C carriers ($p = 0.039$). Furthermore, 5HTTLPR L/L carriers had a higher depression level compared to S/S carriers ($p = 0.027$).

Post hoc tests were performed in order to compare groups of murderers and thieves. No difference was found in the genotype distributions of murderers and thieves or in depression levels (p = 0.977). Interestingly, the only BDHI scale that showed a significant difference between murderers and thieves was "guilt" (Table 5).

Discussion

In this study, we examined a possible contribution of 6 functional genetic polymorphisms in 5 key genes encoding the brain 5-HT system, such as TPH2, SLC6A4, HTR1A, *HTR2C*, and TDO2, to a predisposition to severe criminal offensive behavior in criminal males from the Russian population. Two of these polymorphisms, i.e., 5HTTLPR in SLC6A4 and rs6318 in *HTR2C* genes, showed an association, reaching a significance level after Bonferroni adjustment.

Limitations and Strengths of Our Study

It was disappointing to find out that our expectations concerning possible differences between prisoners convicted for murder or theft were not confirmed. Hardly any differences were found with respect to psychological measures (BDHI and BDI). Another limitation is the probable differences between the sociological characteristics of prisoners and control subjects. When accepting the assumption that the current circumstances of certain social classes may increase the likelihood of being convicted of a felony due to living circumstances or a lack of juridical support, it is difficult to select comparators who are not at a similar risk of being imprisoned in the future. Finally, the sample size is rather limited for a genetic study.

Our study also has important strengths. As far as we know, this is the first genetic study of male Siberian criminal offenders. They were all Caucasian, which makes it a very interesting population to study. To our knowledge, there exist 5 studies of male criminal offenders: one Korean [47], one Czechian [48], one from the Southern USA [49], one Italian [50, 51], and one in a Finnish population [52]. Haeffel et al. [53] studied the relationship of poly-

Table 3. BDHI subscale scores for different genotype carriers in prisoners

Genotype	Assault	Indirect hostility	Irritability	Negativism	Resentment	Suspicion	Verbal hostility	Guilt	Hostility index	Aggression index
5HTTLPR										
L/L	5.8±0.3	4.5±0.2	4.6±0.3	2.5±0.2	4.7±0.3	5.6±0.3	6.8±0.3	6±0.3	10.5±0.5	16.9±0.6
L/S	5.9±0.4	4.1±0.2	4.6±0.2	2.3±0.2	4.4±0.2	5.1±0.3	7.1±0.3	5.9±0.3	9.7±0.5	17.3±0.7
S/S	6.2±0.5	4.2±0.3	4.7±0.5	2.6±0.3	4±0.5	5.5±0.4	7.3±0.5	6±0.4	10±0.8	17.5±1
p	0.839	0.403	0.962	0.526	0.369	0.419	0.654	0.984	0.469	0.880
STin2										
10/10	6.1±0.5	3.9±0.3	4±0.3	2.3±0.2	4.5±0.4	5.5±0.4	6.3±0.4	5.7±0.4	10.4±0.7	15.7±0.8
12/10	5.7±0.2	4.3±0.2	4.5±0.3	2.5±0.2	4.6±0.3	5.2±0.3	6.9±0.3	6.2±0.3	9.8±0.5	17.1±0.6
12/12	6±0.4	4.6±0.2	4.9±0.3	2.5±0.2	4.2±0.2	5.4±0.2	7.4±0.4	5.9±0.3	10±0.5	17.6±0.7
p	0.664	0.234	0.213	0.454	0.640	0.796	0.148	0.611	0.777	0.276
rs6295										
C/C	5.6±0.4	4.1±0.2	5.1±0.3	2.1±0.3	4.7±0.4	5.6±0.4	7.1±0.4	6.1±0.4	10.4±0.7	17.7±0.8
C/G	6.2±0.3	4.7±0.2	4.4±0.3	2.6±0.2	4.6±0.2	5.5±0.3	6.8±0.3	6.1±0.3	10.5±0.5	16.6±0.7
G/G	5.4±0.3	3.9±0.3	4.5±0.3	2.2±0.2	3.8±0.3	4.9±0.4	7±0.4	5.6±0.3	8.8±0.6	16.8±0.7
p	0.224	0.096	0.299	0.100	0.139	0.460	0.823	0.535	0.088	0.573
rs4570625										
T/T	6.1±0.5	3.4±0.5	5.3±0.6	2.4±0.4	5±0.7	6.6±0.9	6.8±0.8	6±0.7	11.6±1.3	18.1±1
G/T	5.9±0.3	4.1±0.2	4.3±0.3	2.2±0.2	4.4±0.3	5.3±0.3	6.9±0.3	5.8±0.3	9.9±0.4	16.7±0.6
G/G	5.9±0.3	4.5±0.2	4.8±0.2	2.5±0.2	4.4±0.2	5.3±0.3	7.1±0.3	6.2±0.2	10±0.4	17.3±0.6
p	0.969	0.097	0.257	0.321	0.732	0.265	0.877	0.586	0.466	0.684
rs6318										
G	5.9±0.2	4.3±0.2	4.6±0.2	2.5±0.1	4.4±0.2	5.5±0.2	6.9±0.2	5.9±0.2	10.1±0.3	17.1±0.5
C	6.1±0.7	4.5±0.4	4.4±0.5	1.9±0.3	4.6±0.5	4.9±0.5	6.9±0.5	6.3±0.5	9.9±1	16±1
p	0.687	0.623	0.687	**0.039**	0.744	0.291	0.829	0.545	0.377	0.865
rs2271537										
A/A	6.5±0.5	4.4±0.4	5±0.3	2.6±0.2	4.3±0.4	5.8±0.3	7.3±0.4	6.3±0.4	10.4±0.6	17.9±0.9
A/C	5.7±0.2	4.5±0.2	4.6±0.2	2.4±0.2	4.4±0.2	5.1±0.3	7±0.3	6.2±0.3	9.7±0.4	17±0.6
C/C	6±0.4	4.1±0.2	4.5±0.4	2.2±0.2	4.7±0.4	5.5±0.3	6.9±0.4	5.6±0.3	10.5±0.6	17±0.8
p	0.325	0.596	0.561	0.330	0.734	0.370	0.874	0.327	0.529	0.733

BDHI, Buss-Durkee Hostility Inventory. Bold is only used to highlight those cases with *p* value <0.05 for the convenience of readers.

morphisms of the dopamine transporter gene and perceived maternal rejection at the onset of major depressive disorder in male adolescents (n = 176) recruited from a juvenile detention center in northern Russia. Retz et al. [54, 55] concentrated on the functional polymorphism of the *5HTT* promoter gene (5HTTLPR) and its impact on ADHD psychopathology in young German adult delinquents. Our imprisoned population is probably more severely disturbed than the persons studied by the other authors.

Role of the 5-HT Transporter in Aggression

Previous studies have revealed that the 5HTTLPR polymorphism may be related to aggression and antisocial behavior [39]. In their meta-analysis of association studies, those authors observed a moderate, positive association between the short S allele of 5HTTLPR and antisocial behavior (OR = 1.41; 95% CI 1.26–1.59). However, a significant heterogeneity in the results of these studies was obvious, which is probably a good explanation for why we obtained dissimilar results. The human *5HTT* gene (SLC6A4) contains a 22-bp repeat element (5HTTLPR) with a 44-bp insertion/deletion resulting in "long" and "short" (16- and 12-bp, respectively) variants [39, 56]. The homozygous long (L/L) genotype results in an increased SLC6A4 transcriptional efficiency compared to the heterozygous (L/S) or homozygous short (S/S) genotypes [36, 39, 56, 57]. The increase in the transcriptional efficiency

Table 4. Depression level according to BDI scores in different genotype carriers in criminals

Polymorphism	Genotype			*p*	
5HTTLPR in *SLC6A4*	LL 15.3±1	LS 14.7±1	SS 10±1	**0.035**	*p* (LL/SS) = **0.027** *p* (LL/LS) = 0.129 *p* (LS/SS) = 0.6
STin2 in *SLC6A4*	10/10 15±1.6	12/10 13.8±1	12/12 14.4±1	0.67	
–1019C>G (rs6295) in *HTR1A*	C/C 14.8±1.4	C/G 13.5±1	G/G 14.4±1.5	0.657	
–703G>T (rs4570625) in *TPH2*	TT 10.2±2.4	GT 14.4±1.3	GG 14.6±0.9	0.375	
rs6318 in HTR2C	G 14.1±0.8		C 16.9±2	0.217	
rs2271537 in *TDO2*	AA 12.5±1.5	AC 14.9±1	CC 15.7±1.3	0.225	

Kruskal-Wallis test and Mann-Whitney test with Bonferroni correction. BDI, Beck Depression Inventory. Bold is only used to highlight those cases with *p* value <0.05 for the convenience of readers.

of the L/L genotype appears to result in a lowered 5-HT concentration in the synaptic cleft and consequently less stimulation of excitatory HTR2C and other 5-HT receptors. It may be related to aggression and antisocial behavior [39], while the short allele is usually associated with such negative characteristics as violence [38, 40].

In our study, the L/L genotype of 5HTTLPR in the *5HTT* gene in Caucasians was more frequent in both groups of criminals (murderers and thieves) than in the control males with no criminal records. Furthermore, 5HTTLPR L/L carriers showed a higher depression level in comparison with S/S carriers. This finding is in good agreement with the predicted antidepressant effect of the deficit of transporter functional activity in S/S carriers. At the same time, other authors have associated the S allele with a predisposition to criminal behavior in the Han population [40]. The discrepancy between our data and those of Liao et al. [40] suggests an interaction between 5HTT genes and some ethnic genetic factors.

Table 5. Comparison of BDHI subscale scores of murderers and thieves

Scale	Murderers	Thieves	*p*
Assault	6.1±0.3	5.5±0.3	0.100
Indirect hostility	4.3±0.18	4.3±0.22	0.931
Irritability	4.5±0.23	4.9±0.25	0.291
Negativism	2.4±0.1	2.4±0.2	0.811
Resentment	4.5±0.2	4.4±0.2	0.818
Suspicion	5.4±0.2	5.4±0.3	0.833
Verbal hostility	7.2±0.2	6.8±0.3	0.289
Guilt	5.7±0.2	6.5±0.2	**0.023**
Hostility index	10.3±0.4	9.8±0.4	0.426
Aggression index	17.2±0.5	17.1±0.6	0.915

BDHI, Buss-Durkee Hostility Inventory. Bold is only used to highlight those cases with *p* value <0.05 for the convenience of readers.

Role of the 5-HT2C Receptor in Aggression

The HTR2C is mainly located in cortical areas, the hippocampus, the striatum, the septum, the thalamus, midbrain nuclei, the spinal cord, and, particularly, the choroid plexus [58]. The excitatory HTR2C has an inhibitory effect within the dorsal striatum (by activating fast spiking GABAergic interneurons) and probably activates the amygdaloid complex (by activating cortical pyramidal cells and nuclear GABAergic projection neurons). The dorsal extrapyramidal circuits with the caudate nucleus as a first relay station regulate the activity of the dorsolateral prefrontal cortex [32]. True activation of the basolateral part of the amygdaloid complex enhances the emotional flight/fight response [21, 22], while inverse activation of caudate HTR2C increases cognitive functioning and decreases defensive aggression. Clozapine, a very effective HTR2C inverse receptor agonist [59], reduced vi-

olence and persistent aggression in patients with schizophrenia and other psychiatric disorders [60]. According to our data, carriers of the rs6318 G allele had lower scores on the "negativism" scale of the BDHI compared with the more frequent C-allele carriers ($p = 0.039$). This could be related to the role of HTR2C within the "cognitive" extrapyramidal circuits which includes the caudate nucleus and targets the prefrontal cortex. Taken together with the fact that negativism reflects a propensity to opposition consisting of passive resistance or an active struggle against the established customs and laws [61], this result could be quite interesting.

Stimulation of HTR2C decreased dopaminergic stimulation of the dorsal striatum (caudate nucleus and putamen) and also increased prefrontal control due to direct activation of glutamatergic and monoaminergic neurons. Within ganglionic areas of the amygdaloid complex HTR2C were found on GABAergic neurons [62].

The *HTR2C* gene is located on the X chromosome, (Xq24 site), so males are hemizygous for cysteine (G) or serine (C) in the 23rd position. However, the functional consequences of this polymorphism are debated. The Cys23Ser variant (rs6318) of the *HTR2C* gene polymorphism is located on the extracellular N-terminus of the HTR2C protein, potentially altering the protein's structure or stability by eliminating a disulfide bond [31]. The findings of Lappalainen et al. [31] and Fentress et al. [63] do not support functional consequences of the C23S SNP in the *HTR2C*. However, Okada et al. [64] found that the Ser23 variant appears to be constitutively more active than Cys23. Jahnsen and Uhlèn [65] localized the C23S site within a cleavable signal peptide of the synthetized receptor protein. Cleaving of the signal peptide is important for translocation of the wild-type receptor to the plasma membrane, but they concluded that the site is probably absent from the mature HTR2C.

Our statistical analysis showed a higher frequency of C-carriers of the rs6318 polymorphism in the HTR2C gene in the group of criminals compared to the control probands. Interestingly, Banlaki et al. [66] studied 887 subjects (45.8% males and 54.2% females), all belonging to the middle socioeconomic class, and examined the possible contribution of 55 SNP to aggressive tendencies measured by the Buss-Perry Aggression Questionnaire. They did not observe any association between aggression and 3 variants of the HTR2C gene (including rs6318) [66]. However, those authors studied other psychological phenomena than we did in our study.

It should be kept in mind that positive associations between this polymorphism and disease states may be a consequence of linkage equilibrium with another SNP that is involved in the disease.

Comparison of the Two Groups of Prisoners

Based on the current opinion that direct physical aggression (murder) has a biological background which differs from that of indirect aggression (theft), we studied persons convicted of these 2 types of crimes separately. However, our results did not reveal any differences in polymorphism distribution. In terms of psychological data, only the "guilt" score in thieves seem to be higher than in murderers. This result, contradictory at first glance, may be explained from different points of view. Criminals, among whom this research was carried out, stayed a long time in the specific conditions of social isolation (1 year or more in a penitentiary facility with strict administrative and subcultural sanctions for acts of aggression). Criminal investigation, arrest, and imprisonment correct aggressive behavior to a great extent. Staying in the company of aggressive personalities also deters aggression, sublimating its manifestation to other forms. Therefore, the level of aggression in prison can significantly differ from the aggression level in the moment of crime commission. However, this does not explain the absence of genetic associations between the 2 groups, because these are primarily related to traits and not so much to states. An assumption exists that while the tendency of an individual toward criminal behavior can be determined by biological factors, the probability of highly aggressive destructive behavior in the form of homicide is defined by personal, social characteristics and individual predisposition, "the de-tabooing of evil" [67, 68]. According to Moyer [69], heredity can determine the personal threshold beyond which the activation of specific neurophysiologic reactions associated with aggressive behavior begins. Mednick et al. [70] showed that adopted children of previously convicted biological parents had a higher risk of criminal behavior, but the types of crimes committed by adopted children and their biological parent did not correlate. Consequently, the type of crime seems not to be genetically determined, but some neurophysiological traits that can lead to antisocial behavior (e.g., impulsivity), may have a biological basis. In our study both murderers and thieves had numerous previous convictions, which indicates an antisocial pattern of behavior. The group of murderers was composed only of men who committed the crime impulsively, not premeditatedly. The group of thieves seems to have a higher "guilt" score, and this can indirectly reflect some personality traits more common in murderers, which can lead to a higher risk of an aggressive

act in a form of homicide. Therefore, our data corroborate the suggestion that 5HTT and the HTR2C are implicated in the predisposition to criminal offensive behavior, but they could not be used as markers of a specific type of aggression. At the same time, the investigation should be supported by an evaluation of more neurophysiology-related characteristics, such as an impulsivity, personality traits, etc. Moreover, these psychological characteristics should be disentangled according to their relation to specific neurobiological functions such as medial prefrontal control over the amygdala, and the likelihood of initiation of an adversity-fleeing (defensive) response or initiation a reward-seeking (offensive) response.

Our study was limited to five 5-HT-related genes, while other important genes, such as those coding for the 5-HT2A receptor (HTR2A) and MAO A, were uninvestigated. At the same time, activation of HTR2A increases dopaminergic transmission within the ventral striatum (nucleus accumbens) and decreases prefrontal control due to the activation of inhibitory fast-spiking GABAergic interneurons. This combination would result in increased impulsivity. Within the cortical parts of the amygdaloid complex, HTR2A are present on glutamatergic pyramidal neurons and on inhibitory GABAergic interneurons and GABAergic projection neurons [62]. Hence, stimulation of HTR2A within the amygdaloid complex would have mixed effects. Banlaki et al. [66] showed an association between aggression and the rs7322347 polymorphism in the HTR2A gene. In our population, higher activity of the 5HTT resulting in less activation of HTR2A, is probably having quite unpredictable effects and the fact that our findings contrast with the median effect found in the meta-analysis of Ficks and Waldman [39] are very well in line with this.

Hereditary deficiency of MAO A produced aggressive and antisocial behavior in humans [27] and increased intermale aggression in mice [71]. Moreover, there is a common VNTR polymorphism affecting MAO A expression in vitro [72, 73]. These functional polymorphisms in HTR2A and MAO A genes could be prospective targets for future studies of differentiation between murderers and thieves.

Conclusion

This study demonstrates the implication of the brain 5-HT system in the mechanisms of genetic predisposition to criminal antisocial behavior. An association of 5HTTLPR in 5-HT transporter (*5HTT*) and rs6318 in 5-HT2C receptor (*HTR2C*) genes with criminality, aggression-related traits, and depression was found. This result contributes to the theory that 5HTT and HTR2C are involved in biological mechanisms of antisocial criminal behavior. However, the lack of biological differences between the 2 groups of prisoners (murderers and thieves) indicates that these members of the 5-HT family do not differentiate between the type and the severity of the crime committed. In the future, other specific elements in the brain 5-HT system (e.g., MAO A and the 5-HT2A receptor) as well as offensive versus defensive backgrounds of aggressive behavior should be considered when studying the genetics of criminal behavior.

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Author Contributions

S.A.I. conceived, designed, coordinated, and supervised this study. V.A.T. and S.A.I. wrote the study protocol after reviewing the literature. V.A.T. monitored this study and collected clinical data and biological samples. V.A.T., Y.B., A.V.K., and E.V.M. genotyped the samples and recorded all of the data in an Excel data base. S.I.G. and M.V.T. did the clinical work. N.A.B. supervised and discussed the clinical work. O.Yu.F., N.K.P., and S.A.I. supervised the technical work. V.A.T. and N.K.P. designed and performed the statistical analysis. Y.B., V.A.T., and A.J.M.L. wrote this paper. S.A.I., V.A.T., J.E.H., O.Yu.F., and B.W. commented on this paper. All of the authors read this paper and agree with its content.

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